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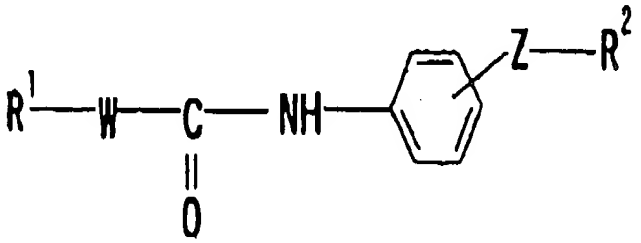
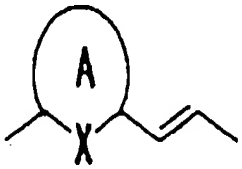
(54) Title: PHARMACEUTICAL COMPOSITION FOR ANTAGONIZING CCR5 COMPRISING ANILIDE DERIVATIVE

(57) Abstract

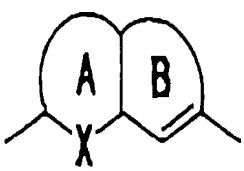
This invention is to provide a pharmaceutical composition for antagonizing CCR5 which comprises a compound of formula (I) wherein R^1 is an optionally substituted 5- to 6-membered ring; W is a divalent group of formula (a) or (b) wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted C, N or O atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group, R^2 is an optionally substituted amino group in which a nitrogen



(1)



(a)



(b)

DESCRIPTION

Pharmaceutical Composition for Antagonizing CCR5 comprising Anilide Derivative

Technical Field

The present invention relates to a pharmaceutical composition for antagonizing CCR5 comprising an anilide derivative.

Background Art

Recently, HIV (human immunodeficiency virus) protease inhibitors are developed for method of the treatment of AIDS (acquired immunological deficient syndrome) and use of the protease inhibitors in combination with conventional two HIV reverse transcriptase inhibitors provides with a further progress of the treatment of AIDS. However, these drugs and their combination use are not sufficient for the eradication of AIDS, and development of new anti-AIDS drugs having different activity and mechanism are sought for.

As a receptor from which HIV invades to a target cell, CD4 is so far known, and recently CCR5 as a second receptor of macrophage-tropic HIV and CXCR4 as a second receptor of T cell-tropic HIV, each of which is G protein-coupled chemokine receptor having seven transmembrane domains, are respectively found out. These chemokine receptors are thought to play an essential role in establishment and spread of HIV infection. In fact, it is reported that a person who is resistant to HIV infection in spite of several exposures retains mutation of homo deletion of CCR5 gene. Therefore, a CCR5 antagonist is expected to be a new anti-HIV drug. However, so far, there has been no report that a CCR5 antagonist is developed as a therapeutic agent of AIDS.

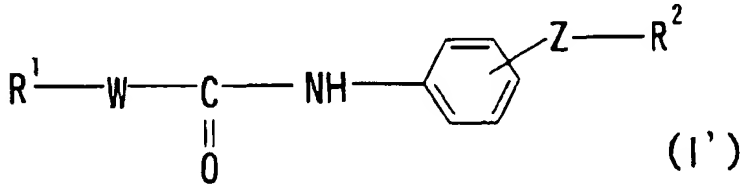
In order to investigate an anti-AIDS drug having CCR5 antagonistic activity, it is necessary to clone CCR5 gene from human tissue derived cDNA library, to ligate said gene

with a vector for expression in animal cells, to introduce said gene into animal cells and to obtain cells expressing CCR5. In addition, with using this transformant, it is necessary to screen a compound which strongly inhibits binding of CC chemokine RANTES, natural ligand, to CCR5 (which strongly antagonizes CCR5). However, so far there has been no report on a low molecule compound having CCR5 antagonistic activity. The present invention is to provide a pharmaceutical composition which is useful for the treatment or prophylaxis of infectious disease of HIV and, in particular, AIDS and which comprises an anilide derivative having CCR5 antagonistic activity.

Disclosure of Invention

The present inventors diligently made extensive studies on compounds having CCR5 antagonistic activity and, as a result, they found that an anilide derivative of the following formula (I') or a salt thereof [hereinafter, referred to as Compound (I')] unexpectedly possesses potent CCR5 antagonistic activity and clinically desirable pharmaceutical effect (e.g. remarkable inhibition of HIV infection to human peripheral mononuclear cells, etc.). Based on the finding, the present invention was accomplished.

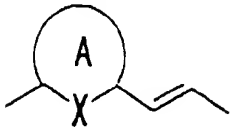
More specifically, the present invention relates to (1) a pharmaceutical composition for antagonizing CCR5 (or a pharmaceutical composition for inhibiting binding of a ligand to CCR5 or a pharmaceutical composition for antagonizing binding of a ligand of CCR5 to CCR5) which comprises a compound of the formula (I'):



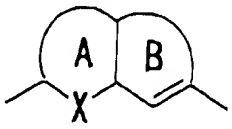
(I')

wherein R^1 is an optionally substituted 5- to 6-membered ring,

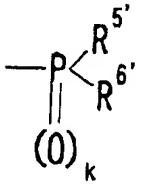
W is a divalent group of the formula:



or



wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, the ring B is an optionally substituted 5- to 7-membered ring, Z is a chemical bond or a divalent group, R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and $R^{5'}$ and $R^{6'}$ are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and $R^{5'}$ and $R^{6'}$ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof;

(2) a composition of the above (1), wherein R^1 is benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, each of which may be substituted;

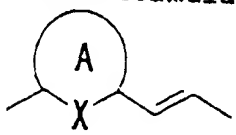
(3) a composition of the above (1), wherein R^1 is an optionally substituted benzene;

(4) a composition of the above (1), wherein the ring A is

furan, thiophene, pyrrole, pyridine or benzene, each of which may be substituted;

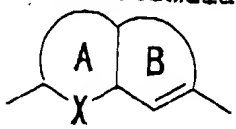
(5) a composition of the above (1), wherein the ring A is an optionally substituted benzene;

(6) a composition of the above (1), wherein W is a group of the formula:



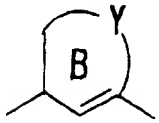
wherein each symbol is as defined in the above (1);

(7) a composition of the above (1), wherein W is a group of the formula:



wherein each symbol is as defined in the above (1);

(8) a composition of the above (7), wherein the ring B is a 5- to 7-membered ring group of the formula:



wherein Y is $-Y'-(CH_2)_m-$ (Y' is -S-, -O-, -NH- or $-CH_2-$, and m is an integer of 0-2), -CH=CH- or -N=CH-), which may have a substituent at any possible position;

(9) a composition of the above (8), wherein Y is $-Y'-(CH_2)_2-$ (Y' is -S-, -O-, -NH- or $-CH_2-$);

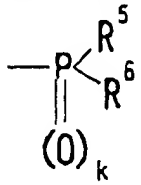
(10) a composition of the above (8), wherein Y is $-(CH_2)_2-$, $-(CH_2)_3-$ or $-O-(CH_2)_2-$;

(11) a composition of the above (10), wherein the ring A is an optionally substituted benzene;

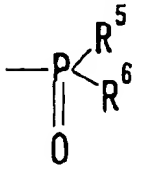
(12) a composition of the above (1), wherein Z is an optionally substituted C_{1-3} alkylene;

(13) a composition of the above (1), wherein Z is a divalent group of the formula: $-Z'-(CH_2)_n-$ (Z' is -CH(OH)-, -C(O)- or $-CH_2-$, and n is an integer of 0-2) in which an optional methylene group may be substituted;

(14) a composition of the above (1), wherein Z is methylene;
(15) a composition of the above (1), wherein Z is substituted at para position of the benzene ring;
(16) a composition of the above (1), wherein R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R^5 and R^6 are independently an optionally substituted hydrocarbon group or an optionally substituted amino group, and R^5 and R^6 may bind to each other to form a cyclic group together with the adjacent phosphorus atom;
(17) a composition of the above (1), wherein R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium or (3) a group of the formula:



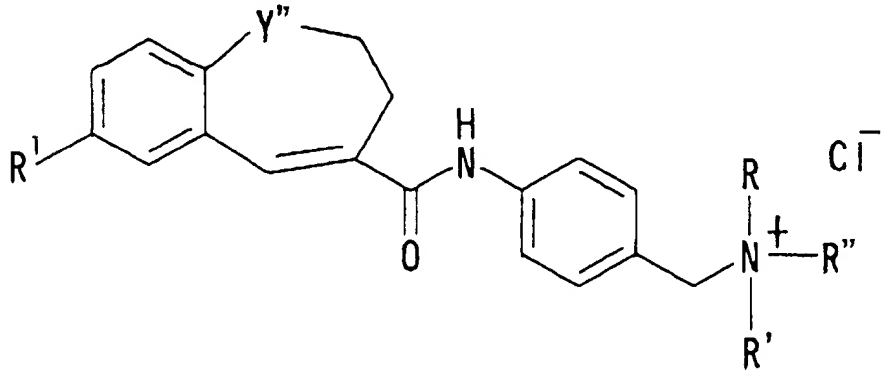
wherein R^5 and R^6 are independently an optionally substituted hydrocarbon group, and R^5 and R^6 may bind to each other to form a cyclic group together with the adjacent phosphorus atom;

(18) a composition of the above (1), wherein R^2 is an optionally substituted amino group wherein a nitrogen atom may form a quaternary ammonium;

(19) a composition of the above (1), wherein R^2 is a group of the formula: $-N^+RR'R''$

wherein R, R' and R'' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group;

(20) a pharmaceutical composition for antagonizing CCR5 which comprises a compound of the formula:



wherein R^1 is an optionally substituted benzene or an optionally substituted thiophene; Y" is $-CH_2-$, -S- or -O-; and R, R' and R" are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group;

(21) a composition of the above (20), wherein R and R' are independently an optionally substituted acyclic hydrocarbon group;

(22) a composition of the above (20), wherein R and R' are independently an optionally substituted C_{1-6} alkyl group;

(23) a composition of the above (20), wherein R" is an optionally substituted alicyclic hydrocarbon group or an optionally substituted alicyclic heterocyclic ring group;

(24) a composition of the above (20), wherein R" is an optionally substituted C_{3-8} cycloalkyl group;

(25) a composition of the above (20), wherein R" is an

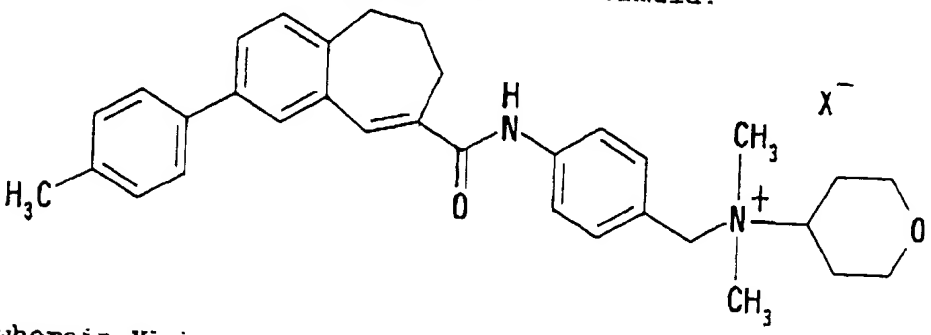
optionally substituted cyclohexyl;

(26) a composition of the above (20), wherein R" is an optionally substituted saturated alicyclic heterocyclic ring group;

(27) a composition of the above (20), wherein R" is an optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted piperidyl;

(28) a composition of the above (20), wherein R" is an optionally substituted tetrahydropyranyl;

(29) a pharmaceutical composition for antagonizing CCR5 which comprises a compound of the formula:



wherein X^- is an anion.

(30) a composition of the above (29), wherein X is a halogen atom;

(31) a pharmaceutical composition for antagonizing CCR5 which comprises

N-methyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-piperidinium iodide,

N-methyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]piperidinium iodide,

N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxmide,

N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]-phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1-benzoxepine-4-carboxmide,

7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzoxepine-4-carboxmide,
N,N-dimethyl-N-[4-[[[2-(4-methylphenyl)-6,7-dihydro-5H-benzocyclohepten-8-yl]carbonyl]amino]benzyl]-N-(tetrahydropyran-4-yl)ammonium iodide,
N,N-dimethyl-N-[4-[[[7-(4-methylphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]-N-(4-oxocyclohexyl)ammonium chloride,
N,N-dimethyl-N-[4-[[[7-(4-ethoxyphenyl)-2,3-dihydro-1-benzoxepin-4-yl]carbonyl]amino]benzyl]-N-(tetrahydropyran-4-yl)ammonium chloride,
or a salt thereof;

(32) a composition of the above (1), which is for the treatment or prophylaxis of infectious disease of HIV;

(33) a composition of the above (1), which is for the treatment or prophylaxis of AIDS;

(34) a composition of the above (1), which is for the prevention of the progression of AIDS;

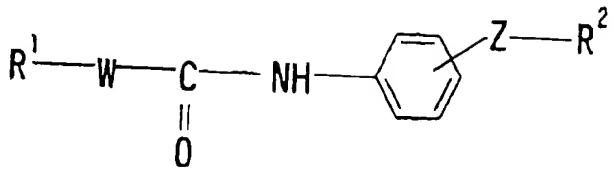
(35) a composition of the above (32), which is used in combination with a protease inhibitor and/or a reverse transcriptase inhibitor;

(36) a composition of the above (35), wherein the reverse transcriptase inhibitor is zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine or delavirdine;

(37) a composition of the above (35), wherein the protease inhibitor is saquinavir, ritonavir, indinavir or nelfinavir;

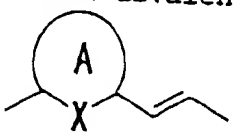
(38) use of the compound of the above (1) or a salt thereof in combination with a protease inhibitor and/or a reverse transcriptase inhibitor for the treatment or prophylaxis of infectious disease of HIV;

(39) a method for antagonizing CCR5 which comprises administering to a mammal in need thereof an effective amount of a compound of the formula:



wherein R^1 is an optionally substituted 5- to 6-membered ring;

W is a divalent group of the formula:



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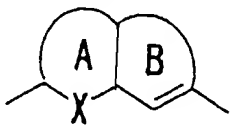
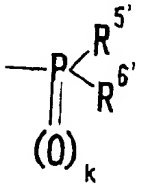
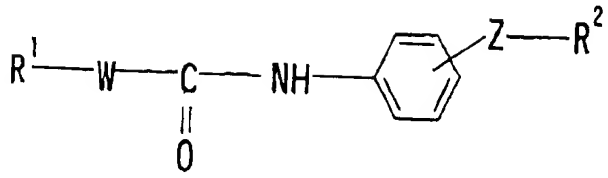


wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



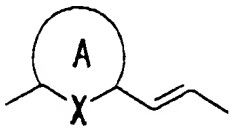
wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and $R^{5'}$ and $R^{6'}$ are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and $R^{5'}$ and $R^{6'}$ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof;

(40) use of a compound of the formula:

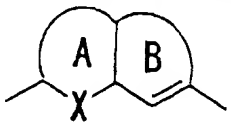


wherein R^1 is an optionally substituted 5- to 6-membered ring;

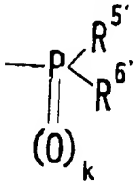
W is a divalent group of the formula:



or



wherein the ring A is an optionally substituted 5- to 6-membered aromatic ring, X is an optionally substituted carbon atom, an optionally substituted nitrogen atom, sulfur atom or oxygen atom, and the ring B is an optionally substituted 5- to 7-membered ring; Z is a chemical bond or a divalent group; R^2 is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and $R^{5'}$ and $R^{6'}$ are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and $R^{5'}$ and $R^{6'}$ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof, for the manufacture of a medicament for antagonizing CCR5; etc.

In the above formula (I'), examples of the "5- to

6-membered ring" of the "optionally substituted 5- to 6-membered ring" represented by R' include a 6-membered aromatic hydrocarbon such as benzene, etc.; a 5- to 6-membered aliphatic hydrocarbon such as cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentanediene, cyclohexanediene, etc.; 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- to 6-membered non-aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran, etc.; etc. Among others, benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran (preferably, 6-membered ring), etc. are preferable, and in particular, benzene is preferable.

Example of the "substituents" which the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R^1 may have include halogen atom, nitro, cyano, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted hydroxy group, an optionally substituted thiol group wherein a sulfur atom may be optionally oxidized to form a sulfinyl group or a sulfonyl group, an optionally substituted amino group, an optionally substituted acyl, an optionally esterified carboxyl group, an optionally substituted aromatic group,

etc.

Examples of the halogen as the substituents for R^1 include fluorine, chlorine, bromine, iodine, etc. Among others, fluorine and chlorine are preferable.

Examples of the alkyl in the optionally substituted alkyl as the substituents for R^1 include a straight or branched C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., and preferably lower (C_{1-4}) alkyl.

Examples of the substituents in the optionally substituted alkyl include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the cycloalkyl in the optionally substituted cycloalkyl as the substituents for R^1 include C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.

Examples of the substituents in the optionally substituted cycloalkyl include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the substituents in the optionally substituted hydroxy group as the substituents for R^1 include

(1) an optionally substituted alkyl (e.g. C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);

(2) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(3) an optionally substituted alkenyl (e.g. C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C_{2-6})alkenyl, etc.);

(4) an optionally substituted cycloalkenyl (e.g. C_{3-7} cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);

(5) an optionally substituted aralkyl (e.g. phenyl-C_{1-4} alkyl (e.g. benzyl, phenethyl, etc.), etc.);

(6) an optionally substituted acyl (e.g. C_{2-4} alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);

(7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituents which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl and (7) optionally substituted aryl may have include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{1-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the

number of the substituents are preferably 1 to 3.

Examples of the substituents in the optionally substituted thiol group as the substituents for R^1 are similar to the above-described substituents in the optionally substituted hydroxy group as the substituents for R^1, and among others,

(1) an optionally substituted alkyl (e.g. C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);

(2) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(3) an optionally substituted aralkyl (e.g. phenyl-C_{1-4} alkyl (e.g. benzyl, phenethyl, etc.), etc.);

(4) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc. are preferable.

Examples of the substituents which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted aralkyl and (4) optionally substituted aryl may have include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the substituents in the optionally substituted amino group as the substituents for R^1 are similar to the above-described substituents in the optionally substituted hydroxy group as the substituents for R^1, and examples of the optionally substituted amino group as the

substituents for R^1 include an amino group which may have one to two substituents selected from the above-described substituents in the optionally substituted hydroxy group as the substituents for R^1, etc. Among others, as the substituents in the optionally substituted amino group as the substituents for R^1,

(1) an optionally substituted alkyl (e.g. C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);

(2) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(3) an optionally substituted alkenyl (e.g. C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C_{2-6}) alkenyl, etc.);

(4) an optionally substituted cycloalkenyl (e.g. C_{3-7} cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);

(5) an optionally substituted acyl (e.g. C_{2-4} alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);

(6) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc. are preferable.

Examples of the substituents, which each of the above-described (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted acyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy

(e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

The substituents in the optionally substituted amino group as the substituents for R^1 may bind to each other to form a cyclic amino group (e.g. 5- to 6-membered cyclic amino, etc. such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.). Said cyclic amino group may have a substituent, and examples of the substituents include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the optionally substituted acyl as the substituents for R^1 include a carbonyl group or a sulfonyl group binding to

(1) hydrogen;

(2) an optionally substituted alkyl (e.g. C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);

(3) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(4) an optionally substituted alkenyl (e.g. C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C_{2-6}) alkenyl, etc.);

(5) an optionally substituted cycloalkenyl (e.g. C_{3-7}

cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
(6) an optionally substituted 5- to 6-membered monocyclic aromatic group (e.g. phenyl, pyridyl, etc.); etc.

Examples of the acyl include acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl, methanesulfonyl, ethanesulfonyl, etc.

Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally substituted cycloalkyl, (4) optionally substituted alkenyl, (5) optionally substituted cycloalkenyl and (6) optionally substituted 5- to 6-membered monocyclic aromatic group may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the optionally esterified carboxyl group as the substituents for R^1 include a carbonyloxy group binding to
(1) hydrogen;
(2) an optionally substituted alkyl (e.g. C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-4}) alkyl, etc.);
(3) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(4) an optionally substituted alkenyl (e.g. C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl,3-hexenyl, etc., preferably lower (C_{2-6}) alkenyl, etc.);
(5) an optionally substituted cycloalkenyl (e.g. C_{3-7} cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
(6) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc., and preferably carboxyl, lower (C_{1-6}) alkoxycarbonyl, aryloxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, phenoxycarbonyl, naphthoxycarbonyl, etc.), etc.

Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally substituted cycloalkyl, (4) optionally substituted alkenyl, (5) optionally substituted cycloalkenyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-6} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the aromatic group in the optionally substituted aromatic group as the substituents for R^1 include 5- to 6-membered homocyclic or heterocyclic ring aromatic ring, etc. such as phenyl, pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, etc.

Examples of the substituents for these aromatic group include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C_{1-4} alkyl (e.g.

trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

The number of the above-mentioned substituents for R^1 is 1-4 (preferably 1-2) and they may be same or different and present at any possible position on the ring represented by R^1. When two or more substituents are present on the 5- to 6-membered ring in the "an optionally substituted 5- to 6-membered ring" represented by R^1, two substituents among them may bind to each other to form a lower (C_{1-6}) alkylene (e.g. trimethylene, tetramethylene, etc.), a lower (C_{1-6}) alkyleneoxy (e.g. $-CH_2-O-CH_2-$, $-O-CH_2-CH_2-$, etc.), a lower (C_{1-6}) alkylenedioxy (e.g. $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, etc.), a lower (C_{2-6}) alkenylene (e.g. $-CH_2-CH=CH-$, $-CH_2-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, etc.), a lower (C_{4-6}) alkadienylene (e.g. $-CH=CH-CH=CH-$, etc.), etc.

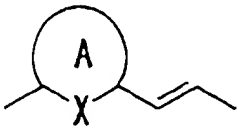
Preferred examples of the "substituents", which the "5- to 6-membered ring" in the "an optionally substituted 5- to 6-membered ring" represented by R^1 may have, include an optionally halogenated lower (C_{1-4}) alkyl (e.g. methyl, ethyl, t-butyl, trifluoromethyl, etc.), an optionally halogenated lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, t-butoxy, trifluoromethoxy, etc.), halogen (e.g. fluorine, chlorine, etc.), nitro, cyano, an amino group optionally substituted with 1-2 lower (C_{1-4}) alkyl groups (e.g. amino, methylamino, dimethylamino, etc.), 5- to 6-membered cyclic amino (e.g. 1-pyrrolidinyl, 1-piperazinyl, 1-piperidinyl, 4-morpholino, 4-thiomorpholino, 1-imidazolyl, 4-tetrahydropyranyl, etc.), etc., and when R^1 is a benzene, the "substituent" is preferably present at para position.

In the above formula (I'), examples of the "5- to 6-membered aromatic ring" in the "optionally substituted 5- to 6-membered aromatic ring" represented by A include

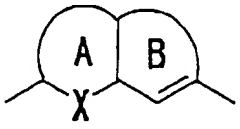
6-membered aromatic hydrocarbon such as benzene, etc.; 5- to 6-membered aromatic heterocyclic ring containing 1 to 3 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; etc. Among others, benzene, furan, thiophene, pyridine (preferably, 6-membered ring) etc. are preferable, and in particular benzene is preferable.

Examples of the "substituents", which the "5- to 6-membered aromatic ring" in the "optionally substituted 5- to 6-membered aromatic ring" represented by A may have, are similar to the "substituents" which the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R^1 may have. The number of said substituents for the ring A is 1-4 (preferably 1-2), and they may be same or different and present at any possible position (e.g. the position of the group X and the other positions) on the ring represented by A.

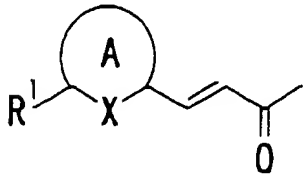
In the above formula (I'), a group of the formula:



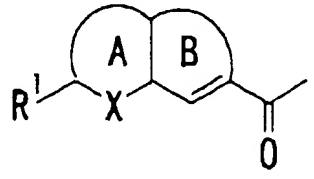
or



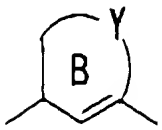
represented by W binds to adjacent groups in the following manner:



or



In the above formula (I'), examples of the "5- to 7-membered ring" in the "optionally substituted 5- to 7-membered ring" represented by B include a 5- to 7-membered ring group of the formula:



, which may have a substituent at any possible position, etc.

In the above formula, the divalent group represented by Y may be any divalent group as far as the ring B forms an optionally substituted 5- to 7-membered ring, and preferred examples of the divalent groups include (1) $-(CH_2)_{a1}-O-(CH_2)_{a2}-$ (a_1 and a_2 are same or different and 0, 1 or 2, provided that the sum of a_1 and a_2 is 2 or less), -O-(CH=CH)-, -(CH=CH)-O-; (2) $-(CH_2)_{b1}-S-(CH_2)_{b2}-$ (b_1 and b_2 are same or different and 0, 1 or 2, provided that the sum of b_1 and b_2 is 2 or less), -S-(CH=CH)-, -(CH=CH)-S-; (3) $-(CH_2)_{d1}-$ (d_1 is 1, 2 or 3), $-CH_2-(CH=CH)-$, $-(CH=CH)-CH_2-$, -CH=CH-; (4) $-(CH_2)_{e1}-NH-(CH_2)_{e2}-$ (e_1 and e_2 are same or different and 0, 1 or 2, provided that the sum of e_1 and e_2 is 2 or less), -NH-(CH=CH)-, -(CH=CH)-NH-, $-(CH_2)_{e6}-(N=CH)-(CH_2)_{e7}-$, $-(CH_2)_{e7}-(CH=N)-(CH_2)_{e6}-$ (one of e_6 and e_7 is 0, and the other is 1), $-(CH_2)_{e8}-(N=N)-(CH_2)_{e9}-$ (one of e_8 and e_9 is 0, and the other is 1); etc. More preferred examples of the divalent groups include -O-, $-O-CH_2-$, $-O-CH_2-CH_2-$, -O-CH=CH-, -S-, $-S-CH_2-$, $-S-CH_2-CH_2-$, -S-CH=CH-, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, -CH=CH-, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, -NH-, -N=CH-, -CH=N-, -N=N- (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc.

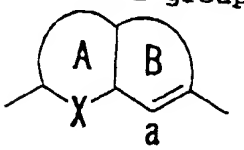
The divalent group may have a substituent. Examples of the substituent include those for the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R^1 and an oxo group, etc. Among others, a lower (C_{1-3}) alkyl (e.g. methyl, ethyl, propyl, etc.), a phenyl group, an oxo group, a hydroxy group, etc. are preferable. In addition, the divalent group may be -O-C(O)- (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc.

The number of the substituents are preferably 1 to 4 (preferably, 1-2), and they may be same or different and bind to the divalent group at any possible position.

As the divalent group represented by Y, a group of the formula: $-Y'-(CH_2)_m-$ (Y' is -S-, -O-, -NH- or $-CH_2-$, and m is an integer of 0-2), -CH=CH-, -N=CH-, $-(CH_2)_m-Y'-$ (Y' is -S-, -O-, -NH- or $-CH_2-$, and m is an integer of 0-2), -CH=N- (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc. is preferable. Among others, a group of the formula: $-Y'-(CH_2)_m-$ (Y' is -S-, -O-, -NH- or $-CH_2-$, and m is an integer of 0-2), -CH=CH-, -N=CH- (in which each of the above formulas represent that it binds to the ring A through its left chemical bond), etc. is preferable. In particular, Y is preferably a group of the formula: $-Y'-(CH_2)_2-$ (Y' is -S-, -O-, -NH- or $-CH_2-$ (preferably -S-, -O- or $-CH_2-$, more preferably -O- or $-CH_2-$)) in which the formula binds to the ring A through its left chemical bond, etc.; and the ring B is preferably a 7-membered ring. As the divalent group represented by Y, a group of the formula: $-(CH_2)_2-$, $-(CH_2)_3-$ or $-O-(CH_2)_2-$ is preferable.

Examples of the "substituents", which the "5- to 7-membered ring" in the "optionally substituted 5- to 7-membered ring" represented by B may have, include those for the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R^1 and an oxo group, etc. The number of the substituents are preferably 1 to 4 (preferably, 1-2), and they may be same or different and bind to the divalent group at any possible position.

In a group of the formula:



represented by W, a carbon atom at the position a is preferably unsubstituted.

In the above formula (I'), examples of the divalent group represented by Z include an optionally substituted divalent group whose straight chain is constituted by 1 to 4 carbon atoms (e.g. C_{1-4} alkylene, C_{2-4} alkenylene, etc., preferably C_{1-3} alkylene, more preferably methylene), etc. The group Z may be bound to any possible position of the benzene ring, and preferably to para position of the benzene ring.

The divalent group represented by Z may be any divalent group whose straight chain is constituted by 1 to 4 atoms and exemplified by an alkylene chain of the formula: $-(CH_2)_{k1}-$ (k_1 is an integer of 1-4), an alkenylene chain of the formula: $-(CH_2)_{k2}-(CH=CH)-(CH_2)_{k3}-$ (k_2 and k_3 are same or different and 0, 1 or 2, provided that the sum of k_2 and k_3 is 2 or less), etc.

Examples of the substituent for the divalent group represented by Z include any one which is capable of binding to the straight chain of the divalent group, and preferably C_{1-6} lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.), lower (C_{3-7}) cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.), an optionally esterified phosphono group, an optionally esterified carboxyl group, hydroxy group, oxo, etc., and more preferably C_{1-6} lower alkyl (preferably C_{1-3} alkyl), hydroxy group, oxo, etc.

Examples of the optionally esterified phosphono group include a group of the formula: $P(O)(OR^7)(OR^8)$ wherein R^7 and R^8 are independently hydrogen, a C_{1-6} alkyl group or a C_{3-7} cycloalkyl group, and R^7 and R^8 may bind to each other to form a 5- to 7-membered ring.

In the above formula, examples of the C_{1-6} alkyl group represented by R^7 and R^8 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc., and examples of the C_{3-7} cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl,